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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,676	HINUMA ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,9 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8, 9 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/26/2008 has been entered.

Status of the claims

2. Claims 8, 9 and 24 are pending and are being examined.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> a. The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 8, 9 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The method steps a-c in the independent claim 8 seem to lack an intermediary step because it is not possible to measure the initial binding of LPA to EDG-2 receptor once the test compound is brought in the measuring mix.

5. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, it is unclear if the animal in part (a) has to have a condition that needs improvement.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claim 9 is rejected under 35 U.S.C. 102(e) as being anticipated by Goddard et al. (U.S. Pat. No. 6,949,528).

Since the EDG-2 receptor is not comprised in the kit claimed, the claim is interpreted as being drawn to a composition comprising lysophosphatidic acid and a buffer. The intended use and the printed instructions are not given patentable weight for the claim.

Goddard et al. teach compositions comprising lysophosphatidic acids and buffers that have set values for their pH (Col. 27, lines 12-26).

Thus, Goddard et al. anticipates claim 9.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 8 and 24 are rejected under 35 U.S.C. 103(a) as obvious over Erickson et al. (U.S. Pat. 6, 485,922, 11/26/2002) in view of Lynch et al. (U. S. Pat. No. 7,169,818) and Inoue CK (Semin. Nephrol., 22,415-422, 2002).

The claims are drawn to a method of screening for a test compound that changes a binding property of lysophosphatidic acid (LPA) to an EDG-2 receptor and that inhibits mesangial cell growth, wherein the EDG-2 receptor comprises the amino acid sequence of SEQ ID NO: 1. The method comprises the following steps:

a) bringing into contact the LPA, the EDG-2 receptor, and the test compound;

b) measuring the binding property of the LPA and the EDG-2 receptor;

c) determining whether the test compound changes the binding property of the LPA and the EDG-2 receptor;

d) bringing into contact a mesangial cell expressing the EDG-2 receptor and the LPA and measuring mesangial cell growth;

e) bringing into contact a mesangial cell expressing the EDG-2 receptor, LPA, and the test compound of step c) determined to change the binding property of the lysophosphatidic acid and the EDG-2 receptor and measuring mesangial cell growth;

f) measuring the effect of the test compound on mesangial cell growth by comparing d) and e); and

g) determining whether the test compound inhibits mesangial cell growth.

Erickson et al. teach a method for identifying compounds which modulate the activity of any of the EDG receptors, comprising the steps of exposing a compound and LPA to the EDG-2 receptor coupled to a response pathway, under conditions and for a

time sufficient to allow interaction of LPA with the EDG-2 receptor and an associated response through the pathway, and b) detecting an increase or a decrease in the stimulation of the response pathway, relative to the absence of the tested compound (col. 6 from line 28 to col. 7, line 42). The Seq. Id. of the receptor mentioned by Erickson et al, Seq. Id No: 20, is identical to Seq. Id. No.: 1 of the instant application. Since the detection of any activation of the EDG-2 receptor is necessarily linked to the binding of the LPA to the EDG-2 receptor, the limitations of claim 8 is present in Erickson et al. Erickson is silent about the use of the method applied to mesangial cells as a two step process and further determination of improvement of renal conditions upon the use of the antagonist.

Lynch et al. teach a method of assaying the binding of agonist or antagonists of LPA for the activation of LPA receptors and thus allow the identification of LPA receptor agonists and antagonists as well as determination of the relative efficacies and potencies at each receptor in a common system. The same results were obtained regardless of whether the recombinant receptor used exogenous G proteins (HEK293T cells) or endogenous G proteins (RH7777 cells) and further the activities measured in the broken cell assay predicted the responses seen in whole cell assays. Thus the primary assay used for compound potency and efficacy is a valid measure of activity at LPA/Edg receptors (col. 4, line 65 to col. line 9). Therefore the reference teaches the confirmation of the results obtained in the absence of living cells in the context of a living cell The findings from the in vitro (broken cells assays) were predictive for the

success of the method in the cell culture assays and thus the method could be reasonable expected to work in animal test also .

Inoue CK teaches that role of LPA in regulating renal mesangial cells growth and apoptosis by stimulating the EDG-2 receptor (p.415, right col. and Fig.3). Also taught is the fact that the inappropriate equilibrium of mesangial cell growth and death resulting from improper blockage of apoptosis induced by LPA is involved in the etiology of glomerulonephritis.

Since the person of ordinary skill in the art would realize, based upon Inoue et al., that blocking the effects of LPA on mesangial cells would have had beneficial effects for the renal diseases in which overgrowth of mesangial cells have been involved, a person of ordinary skill in the art would have been motivated to use the methods of Erickson et al. and Lynch et al. to look for antagonists of LPA with a reasonable expectation of success, given also the teachings of Inoue et al. This is because the method was successfully used to find compounds that inhibited LPA binding to its receptor and the use of mesangial cells would have represented one of the possibilities of testing in conditions in which the receptor would have been part of the cell membrane.

On pages 8-9 of the Remarks submitted with the after final amendment, Applicants argue that Erickson et al. does not teach or suggest all the limitations presented in the amended claims.

The arguments were carefully considered but not found persuasive because the test performed by Erickson et al. and combined with the method of Lynch et al. would

identify compounds that modulate the activity of EDG receptors, both in absence of cell culture and in the presence of cells in culture, would make the instant claims obvious. The fact that cell culture assays were used, it would reasonably be expected for the method to work in animals too. Unless the Applicant presents experimental evidence that the EDG-2 receptor found on mesangial cells is different than the EDG-2 receptor known in the art and claimed by Erickson et al., or Lynch et al., a difference that is nowhere presented in the Specification, the claimed method is no different than the method of Erickson et al. Inhibiting proliferation of mesangial cells by antagonistic action of a compound binding to EDG-2 receptor is linked to signal transduction events which occur in all cells expressing the receptor and is not unique to mesangial cells.

12. Claims 8, 9 and 24 are rejected under 35 U.S.C. 103(a) as obvious over Miller et al. (U.S. Pat. 6,875,757 04/05/2005) in view of Lynch et al. (U. S. Pat. No. 7,169,818) and in further view of Inoue CK (Semin. Nephrol., 22,415-422, 2002).

Miller et al. teach method of modulating LPA activity on an LPA receptor which includes providing a compound which has activity as an LPA receptor antagonist and contacting an LPA receptor with the compound under conditions effective to inhibit LPA-induced activity of the LPA receptor (col. 8, lines 10-40). One of the LPA receptors is EDG-2 (fig. 1). The reference does not explicitly teach about the use of the method applied to mesangial cells, and for further determination of improvement of renal conditions upon the use of the antagonist. Nevertheless, any LPA activity through EDG-2 is in the wake of LPA binding to the EDG-2 receptor and thus the effects on any cells

are expected to still be able to be blocked, irrespective of the cells that harbor the EDG-2 receptor.

The teachings of Lynch et al and Inoue CK were presented *supra*.

Thus, it would have been obvious for a person of ordinary skill in the art to block the effects of LPA on mesangial cells with beneficial effects for the renal diseases in which overgrowth of mesangial cells have been involved with the compounds screened according to the method of Miller et al. and Lynch et al. (which used the methods both for receptors per se and in the context of a cell line) with reasonable expectation of success. This is because the methods of Miler et al. and Lynch et al. were intended to uncover LPA binding blockers in general and it would have the antagonistic effect every where the signal transduction pathways through EDG-2 receptors would have occurred in response to LPA binding. The teachings of Inoue et al. would have motivated a person of ordinary skill in the art to use the mesangial cells for testing for modulators of LPA/EDG-2 interaction. A person of ordinary skill in the art is always motivated to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

On pages 9-10 of the Remarks submitted with the after final amendment, Applicants argue that Miller et al. does not teach or suggest all the limitations presented in the amended claims.

The arguments were carefully considered but not found persuasive because the test performed by Miller et al. would identify compounds that modulate the activity of

LPA receptors and combined with the teachings of Inoue et al and Lynch et al. would make the two step process obvious. Unless the Applicant presents experimental evidence that the EDG-2 receptor found on mesangial cells is different than the EDG-2 receptor known in the art and claimed by Miller et al. or by Lynch et al., a difference that is nowhere presented in the Specification, the claimed method is obvious in view of Miller et al., Lynch et al and Inoue et al.

Conclusion

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/ Ph.D.
Primary Examiner, Art Unit 1647